AN - 1993:73773 CAPLUS
DN - 118:73773
TI - Potent gonadotropin releasing hormone antagonists with low histamine-releasing activity
IN - Nestor, John J., Jr.; Tahilramani, Ram; Ho, Teresa L.; Goodpasture, Jessie C.; Vickery, Brian H.; Ferrandon, Pierre
CS - Inst. Bio-Org. Chem., Syntex Res., Palo Alto, CA, 94304, USA
SO - J. Med. Chem. (1992), 35(21), 3942-8
CODEN: JMCMAR; ISSN: 0022-2623
DT - Journal
LA - English
AB - The incorporation of Arg residues into position 6 of gonadotropin-releasing hormone antagonists had resulted in compds. with increased in vivo potency but also made these analogs potent mast cell degranulators. Substitution of position 8 by hArg(R)2 (NG,NG-dialkylhomoargnine) was examd, based on the hypotheses that the Arg-Pro sequence is of major importance for this histamine-releasing side effect and that shielding of the charge may be an effective way to block degranulation. Analogs in four series were evaluated: (A) [N-Ac-D-Nal(2), 1D-pCl-Phe2,D-Pal(3)3,6,Arg5,hArg(R)28,D-Ala10]GnRH, (B) [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Pal(3)3,6,hArg(R)25,8,D-Ala10]GnRH, (C) [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Pal(3)3,6,hArg(R)28,D-Ala10]GnRH, (D) [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Pal(3)3,D-hArg(R)26,hArg(R)28,D-Ala10]GnRH. Although substitution R = Et2, Bu4, (CH2)3, and (CH2CF3)2 was tested, in each series substitution with hArg(Et)2 gave the best results. Two compds. were considered for clin. evaluation: [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Pal(3)3,6,hArg(Et)28,D-Ala10]GnRH and [N-Ac-D-Nal(2)1,D-pCl-Phe2,D-Pal(3)3, D-hArg(Et)26,hArg(Et)28,D-Ala10]GnRH (ganirelix acetate). These compds. had high potency for ovulation suppression and low histamine-releasing potency in vitro (ED50 = 0.6-0.29 .mu.g/rat and EC50 = 196-13 .mu.g/mL, resp). Ganirelix is currently in Phase II clin. trails and appears to be the most potent GnRH antagonist tested in humans (based upon ED50 for 24-h suppression of testosterone levels).
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LA - English
IT - 79652-02-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction with benzyl(benzyloxycarbonyl)lysine toluenesulfonate)
RN - 79652-02-1 CAPLUS
CN - Thiourea, N,N'-bis(2,2,2-trifluoroethyl)- (9CI) (CA INDEX NAME)

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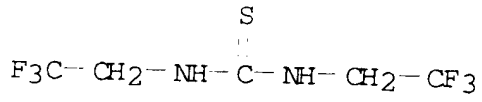

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